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# Gene Section
## Review

# PML (promyelocytic leukemia)

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## Abstract

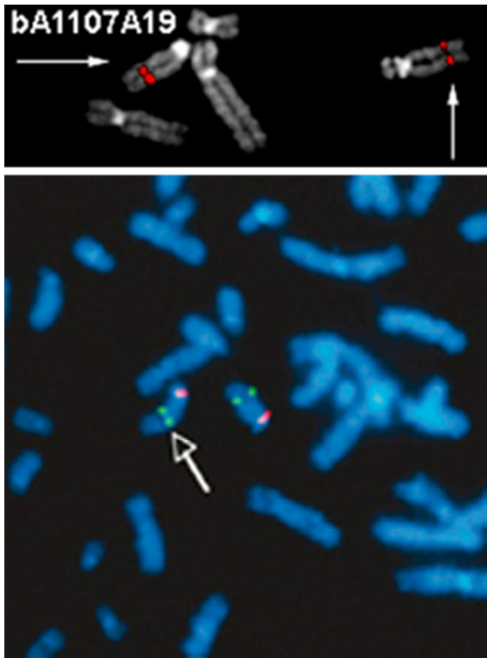
Review on PML, with data on DNA/RNA, on the protein encoded and where the gene is implicated.

## Identity

**Other names:** MYL, RNF71, TRIM19

**HGNC (Hugo):** PML

**Location:** 15q24.1




Top: Courtesy Mariano Rocchi, Resources for Molecular Cytogenetics. Bottom: Metaphase FISH analysis of PML (green); red dots indicate centromere of chromosome 15 (Subramaniyam et al., 2006).

## DNA/RNA

### Description

PML is composed of 9 exons. Exons 7 and 8 can be divided into exons 7a, 7b, 8a and 8b.

### Transcription

Transcription of PML generates 22 transcripts (splice variants) with at least 11 different isoforms (PMLI, PMLIa, PMLII, PMLIIa, PMLIII, PMLIV, PMLIVa, PMLV, PMLVI, PMLVIIa, PMLVIIb). Names of PML isoforms are based on the original nomenclature defined by Jensen et al., 2001.

### Pseudogene

No pseudogenes have been reported so far.

## Protein

### Description

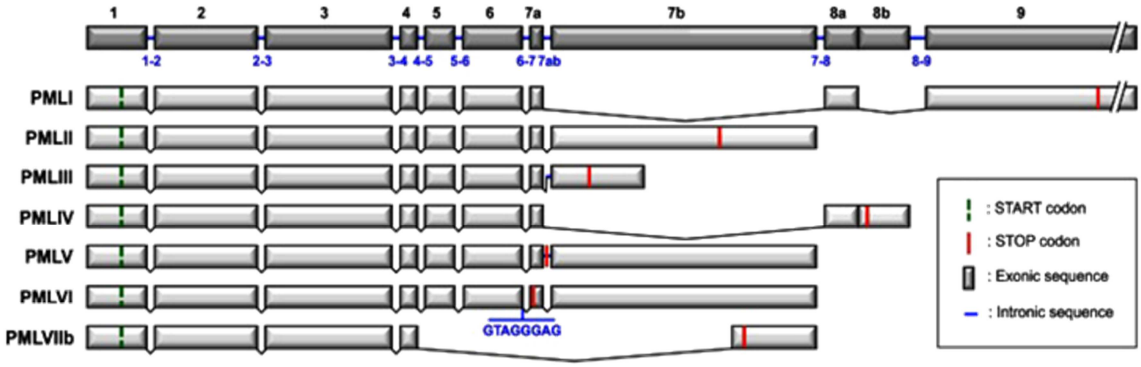
Alternative splicing of PML gives rise to several isoforms with different molecular weight: PMLI is the longest isoform and is composed of 882 amino acids, while the shortest is PMLVIIb (435 amino acids).

PML belongs to the family of the tripartite motif (TRIM).

The RBCC/TRIM motif is present in all PML isoforms and is encoded by the exons 1-3.

The RBCC domain is composed of a RING finger domain (R), two B-boxes domains (B1 and B2) and an α-helical coiled-coil domain (CC).

The RING finger motif is a conserved cysteine-rich zinc-binding domain found in several classes of proteins.

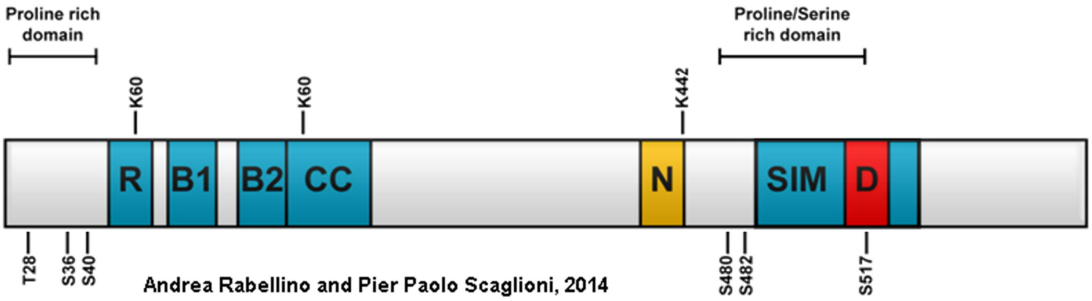



Structural organization of PML human gene (Nisole et al., 2013).


Schematic representation of PML isoforms (Nisole et al., 2013).

The RING domain of PML is involved in the formation of the PML nuclear bodies (PML-NBs, see below) and in several others PML functions. Adjacent to the RING domain lay two cysteine-rich domains named B-boxes: these two domains have been proposed to work as second zinc-binding domain and they are involved in PML-NBs formation and in several others PML functions. The coiled-coil domain mediate PML homo- and hetero-dimerization. The CC domain is also essential for PML-NBs formation and PML functions. A nuclear localization signal (NLS) is present in the isoforms but not in PMLVIIb. The SUMO interacting motif (SIM) of PML is required for the recognition and binding of SUMOylated proteins (Jensen et al., 2001; Nisole et al., 2013). The SIM domain also contains the PML degron, involved in the CK2-dependent PML degradation (Scaglioni et al., 2006). PML undergoes several post-translational modifications. Several kinases phosphorylate PML on serine and threonine residues regulating its functions (Bernardi et al., 2004; Hayakawa and Privalsky, 2004; Scaglioni et al., 2006; Yang et al., 2006). SUMOylation is the most intensely studied post-translational modification of PML. Both SUMO1 and SUMO2/SUMO3 bind covalently to PML. SUMOylation facilitates PML-NBs formation promoting tumor suppressive response PML-dependent, but also promotes leukemogenesis by the SUMOylation of PML-RARA. Finally, SUMOylation also promotes ubiquitin-mediate degradation of PML and PML-RARA (Fu et al., 2005; Shen et al., 2006; Lallemand-Breitenbach et al., 2008; Kamitani et al., 1998a; Kamitani et al., 1998b; Rabellino et al., 2012). Ubiquitination regulates PML functions and activity and deregulation of PML appears to be the common mechanism accounting for PML loss in tumors (reviewed in Rabellino and Scaglioni, 2013). Finally, PML can be also acetylated (Hayakawa et al., 2008).

PML is the major constituent of the PML-NBs. PML-NBs are highly dynamic nuclear structures tightly bound to the nuclear matrix. Several functions of PML are related to the PML-NBs functions (reviewed in Bernardi et al., 2007). More than 150 different proteins have been shown to localize into PML-NBs (Van Damme et al., 2010).




Schematic representation of PML isoform IV protein domains. R = RING-finger domains, aa 55-91; B1, B2 = B-boxes 1 aa 124-166 and 2 aa 184-228; CC = α-helical coiled-coil domain, aa 233-360; N = nuclear localization signal, aa 428-442; SIM = SUMO interacting motif, 508-518; D = degron. The three major SUMOylation sites (K60, K160 and K442) are indicated, as well as the major phosphorylation sites (T28, S36, S40, S480, T482, S517).

## Expression

PML is ubiquitously expressed.

## Localisation

Nuclear (PMLI-VI) and cytoplasmic (PMLVIIb).

## Function

PML has been implicated in several cellular functions.

**Cellular senescence:** PML is a key regulator of cellular senescence. PML is involved in oncogenic-induced senescence (OIS) K-RAS dependent in a p53 dependent way (de Stanchina et al., 2004; Ferbeyre et al., 2000; Pearson et al., 2000; Scaglioni et al., 2012). PML is also involved in Rb-dependent senescence (Mallette et al., 2004).

**Apoptosis:** PML promotes apoptosis primarily by its ability to interact with p53 (Wang et al., 1998). Moreover, a pro-apoptotic function has been also attributed to the cytoplasmic isoform of PML (Giorgi et al., 2010).

**Neoangiogenesis:** PML represses HIF1 transcription, blocking de novo angiogenesis (Bernardi et al., 2006).

**Cell migration:** PML is involved in the regulation of cell migration by the negatively regulating of β-1 integrins (Reineke et al., 2010).

**DNA damage response:** several proteins involved in DNA repair have been report to reside into PML-NBs.

Therefore, PML is also involved in DNA-repair, even though the mechanisms are still not completely clear (reviewed in Dellaire and Bazett-Jones, 2004).

**Anti-viral response:** several viral proteins interact with PML and the PML-NBs; moreover, several reports implicate PML and PML-NBs in anti-viral response (reviewed in Geoffroy and Chelbi-Alix, 2011).

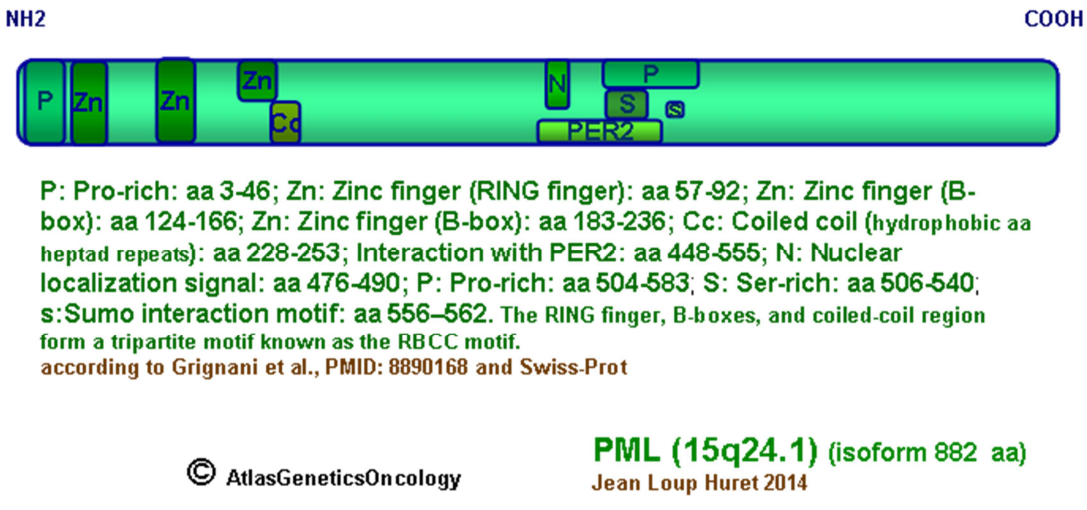
**Hematopoietic stem cell maintenance:** PML has been reported being involved in hematopoietic stem cell maintenance by the regulation of the fatty acid oxidation (Ito et al., 2008; Ito et al., 2012).

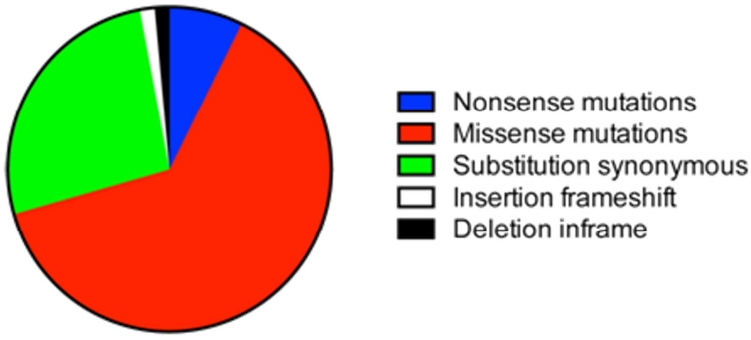
Several functions of PML are related to its ability to form PML-NBs.

PML-NBs have been involved in tumor suppression, senescence and apoptosis, DNA-damage response, cell migration, neoangiogenesis and anti-viral response (reviewed in Bernardi et al., 2007).

## Homology

PML is conserved in Amniota (source: HomoloGene).






Schematic representation of the mutations type of human PML found in human tumor samples (source COSMIC).

# Mutations

**Note**

PML-RARA is the product of the chromosomal translocation t(15;17) and it causes acute promyelocytic leukemia (APL) (de Thé et al., 1990; Goddard et al., 1991; Kakizuka et al., 1991; Pandolfi et al., 1991).

## *Germinal*

No germinal mutations of PML have been reported.

## *Somatic*

At least 65 different somatic mutations have been described. All the informations in this regard can be found at the COSMIC website.

# Implicated in

## *Acute promyelocytic leukemia (APL)*

**Note**

(de Thé et al., 1990; Goddard et al., 1991; Kakizuka et al., 1991; Pandolfi et al., 1991)

**Disease**

The balanced chromosomal translocation t(15;17)(q24;q21) causes APL by driving the synthesis of the PML-RARA oncoprotein. This translocation drives the production of three different PML-RARA variants, depending on the length of the PML module: a short variant PML(S)-RARA, an intermediate variant PML(V)-RARA and a long variant PML(L)-RARA. Generally, 70% of the APL patients carry the PML(L)-RARA variant, followed by the PML(S)-RARA variant (20%) and the PML(V)-RARA (10%) (Melnick and Licht, 1999). PML staining in APL cells show a characteristic pattern commonly named "microspeckles" due to the fact that PML-RARA disrupts the PML-NBs. PML-RARA acts as a transcriptional repressor of RARA target genes. At the same time PML-RARA physically interacts with PML, impairing its tumor-suppressive functions. Combined, these features lead to the aberrant self-renewal of hematopoietic stem cells and block of differentiation of myeloid precursor cells at the promyelocytic stage (de Thé et al., 2012). APL is a distinct subtype of acute myeloid leukemia (AML), is a rare condition though extremely aggressive and malignant.

Clinically, APL symptoms tend to be similar to AML. APL is characterized by a severe coagulopathy, including disseminated intravascular coagulation (DIC).

**Prognosis**

APL is normally treated with the combination of retinoic acid (ATRA) and arsenic trioxide (ATO). This therapy leads to the remission of the disease in more than 90% of the cases. Notably, APL was the first malignant disease cured with targeted therapy (Lo-Coco et al., 2013).

## *B-cell acute lymphoblastic leukemia (B-ALL)*

**Note**

(Nebral et al., 2007; Qiu et al., 2011; Kurahashi et al., 2011)

**Disease**

The transcription factor PAX5 is required for development and maintenance of B-cell. Several chromosomal translocations involving PAX5 have been described, including the t(9;15)(p13;q24) in which the 5' region of PAX5 is fused to PML. So far, two cases of B-ALL PAX5-PML-dependent have been reported. The fused PAX5-PML oncoprotein has a dominant-negative effect on both PML and PAX5, inhibiting PAX5 activation of B-cell specific genes and disrupting PML-NBs formation.

**Prognosis**

Kurahashi and colleagues suggest that B-ALL PAX5-PML dependent could be treated with ATO (Kurahashi et al., 2011).

## *Various cancers*

**Note**

Several reports indicate a reduced PML expression in several cancer types (Gurrieri et al., 2004; Rabellino et al., 2012; Rabellino and Scaglioni, 2013).


**Disease**

PML protein expression was reduced or abolished in prostate adenocarcinomas (63% [95% confidence interval {CI} = 48% to 78%] and 28% [95% CI = 13% to 43%], respectively), colon adenocarcinomas (31% [95% CI = 22% to 40%] and 17% [95% CI = 10% to 24%]), breast carcinomas (21% [95% CI = 8% to 34%] and 31% [95% CI = 16% to 46%]), lung carcinomas (36% [95% CI = 15% to 57%] and 21% [95% = 3% to 39%]), lymphomas (14% [95% CI = 10% to 18%] and 69% [95% CI = 63% to 75%]), CNS tumors (24% [95% CI = 13% to 35%] and 49% [95% CI = 36% to 62%]), and germ cell tumors (36% [95% CI = 24% to 48%] and 48% [95% CI = 36% to 60%]) but not in thyroid or adrenal carcinomas (Gurrieri et al., 2004). In all the cases, PML mRNA levels are comparable to the healthy tissues and the PML gene is rarely mutated, but the protein levels of PML are reduced. This correlates with several reports that underline the role of PML degradation in tumor progression and maintenance (reviewed in Rabellino and Scaglioni, 2013).

**Prognosis**

In most of the cases, loss of PML is associated with tumor progression, like was reported for prostate cancer, breast cancer and CNS tumors (Gurrieri et al., 2004).

# Breakpoints

**Note**

Breakpoint at q24, responsible of translocation t(15;17)(q24;q21).

# References

de Thé H, Chomienne C, Lanotte M, Degos L, Dejean A. The t(15;17) translocation of acute promyelocytic leukaemia fuses the retinoic acid receptor alpha gene to a novel transcribed locus. Nature. 1990 Oct 11;347(6293):558-61

Goddard AD, Borrow J, Freemont PS, Solomon E. Characterization of a zinc finger gene disrupted by the t(15;17) in acute promyelocytic leukemia. Science. 1991 Nov 29;254(5036):1371-4

Kakizuka A, Miller WH Jr, Umesono K, Warrell RP Jr, Frankel SR, Murty VV, Dmitrovsky E, Evans RM. Chromosomal translocation t(15;17) in human acute promyelocytic leukemia fuses RAR alpha with a novel putative transcription factor, PML. Cell. 1991 Aug 23;66(4):663-74

Pandolfi PP, Grignani F, Alcalay M, Mencarelli A, Biondi A, LoCoco F, Grignani F, Pelicci PG. Structure and origin of the acute promyelocytic leukemia myl/RAR alpha cDNA and characterization of its retinoid-binding and transactivation properties. Oncogene. 1991 Jul;6(7):1285-92

Kamitani T, Kito K, Nguyen HP, Wada H, Fukuda-Kamitani T, Yeh ET. Identification of three major sentrinization sites in PML. J Biol Chem. 1998a Oct 9;273(41):26675-82

Kamitani T, Nguyen HP, Kito K, Fukuda-Kamitani T, Yeh ET. Covalent modification of PML by the sentrin family of ubiquitin-like proteins. J Biol Chem. 1998b Feb 6;273(6):3117-20

Wang ZG, Ruggero D, Ronchetti S, Zhong S, Gaboli M, Rivi R, Pandolfi PP. PML is essential for multiple apoptotic pathways. Nat Genet. 1998 Nov;20(3):266-72

Melnick A, Licht JD. Deconstructing a disease: RARalpha, its fusion partners, and their roles in the pathogenesis of acute promyelocytic leukemia. Blood. 1999 May 15;93(10):3167-215

Ferbeyre G, de Stanchina E, Querido E, Baptiste N, Prives C, Lowe SW. PML is induced by oncogenic ras and promotes premature senescence. Genes Dev. 2000 Aug 15;14(16):2015-27

Pearson M, Carbone R, Sebastiani C, Cioce M, Fagioli M, Saito S, Higashimoto Y, Appella E, Minucci S, Pandolfi PP, Pelicci PG. PML regulates p53 acetylation and premature senescence induced by oncogenic Ras. Nature. 2000 Jul 13;406(6792):207-10

Jensen K, Shiels C, Freemont PS. PML protein isoforms and the RBCC/TRIM motif. Oncogene. 2001 Oct 29;20(49):7223-33

Bernardi R, Scaglioni PP, Bergmann S, Horn HF, Vousden KH, Pandolfi PP. PML regulates p53 stability by sequestering Mdm2 to the nucleolus. Nat Cell Biol. 2004 Jul;6(7):665-72

de Stanchina E, Querido E, Narita M, Davuluri RV, Pandolfi PP, Ferbeyre G, Lowe SW. PML is a direct p53 target that modulates p53 effector functions. Mol Cell. 2004 Feb 27;13(4):523-35

Dellaire G, Bazett-Jones DP. PML nuclear bodies: dynamic sensors of DNA damage and cellular stress. Bioessays. 2004 Sep;26(9):963-77

Gurrieri C, Capodieci P, Bernardi R, Scaglioni PP, Nafa K, Rush LJ, Verbel DA, Cordon-Cardo C, Pandolfi PP. Loss of the tumor suppressor PML in human cancers of multiple histologic origins. J Natl Cancer Inst. 2004 Feb 18;96(4):269-79

Hayakawa F, Privalsky ML. Phosphorylation of PML by mitogen-activated protein kinases plays a key role in arsenic trioxide-mediated apoptosis. Cancer Cell. 2004 Apr;5(4):389-401

Mallette FA, Goumard S, Gaumont-Leclerc MF, Moiseeva O, Ferbeyre G. Human fibroblasts require the Rb family of tumor suppressors, but not p53, for PML-induced senescence. Oncogene. 2004 Jan 8;23(1):91-9

Fu C, Ahmed K, Ding H, Ding X, Lan J, Yang Z, Miao Y, Zhu Y, Shi Y, Zhu J, Huang H, Yao X. Stabilization of PML nuclear localization by conjugation and oligomerization of SUMO-3. Oncogene. 2005 Aug 18;24(35):5401-13

Bernardi R, Guernah I, Jin D, Grisendi S, Alimonti A, Teruya-Feldstein J, Cordon-Cardo C, Simon MC, Rafii S, Pandolfi PP. PML inhibits HIF-1alpha translation and neoangiogenesis through repression of mTOR. Nature. 2006 Aug 17;442(7104):779-85

Scaglioni PP, Yung TM, Cai LF, Erdjument-Bromage H, Kaufman AJ, Singh B, Teruya-Feldstein J, Tempst P, Pandolfi PP. A CK2-dependent mechanism for degradation of the PML tumor suppressor. Cell. 2006 Jul 28;126(2):269-83

Shen TH, Lin HK, Scaglioni PP, Yung TM, Pandolfi PP. The mechanisms of PML-nuclear body formation. Mol Cell. 2006 Nov 3;24(3):331-9

Subramaniyam S, Nandula SV, Nichols G, Weiner M, Satwani P, Alobeid B, Bhagat G, Murty VV. Do RARA/PML fusion gene deletions confer resistance to ATRA-based therapy in patients with acute promyelocytic leukemia? Leukemia. 2006 Dec;20(12):2193-5

Yang S, Jeong JH, Brown AL, Lee CH, Pandolfi PP, Chung JH, Kim MK. Promyelocytic leukemia activates Chk2 by mediating Chk2 autophosphorylation. J Biol Chem. 2006 Sep 8;281(36):26645-54

Bernardi R, Pandolfi PP. Structure, dynamics and functions of promyelocytic leukaemia nuclear bodies. Nat Rev Mol Cell Biol. 2007 Dec;8(12):1006-16

Nebral K, König M, Harder L, Siebert R, Haas OA, Strehl S. Identification of PML as novel PAX5 fusion partner in childhood acute lymphoblastic leukaemia. Br J Haematol. 2007 Oct;139(2):269-74

Hayakawa F, Abe A, Kitabayashi I, Pandolfi PP, Naoe T. Acetylation of PML is involved in histone deacetylase inhibitor-mediated apoptosis. J Biol Chem. 2008 Sep 5;283(36):24420-5

Ito K, Bernardi R, Morotti A, Matsuoka S, Saglio G, Ikeda Y, Rosenblatt J, Avigan DE, Teruya-Feldstein J, Pandolfi PP. PML targeting eradicates quiescent leukaemia-initiating cells. Nature. 2008 Jun 19;453(7198):1072-8

Lallemand-Breitenbach V, Jeanne M, Benhenda S, Nasr R, Lei M, Peres L, Zhou J, Zhu J, Raught B, de Thé H. Arsenic degrades PML or PML-RARalpha through a SUMO-triggered RNF4/ubiquitin-mediated pathway. Nat Cell Biol. 2008 May;10(5):547-55

Giorgi C, Ito K, Lin HK, Santangelo C, Wieckowski MR, Lebiedzinska M, Bononi A, Bonora M, Duszynski J, Bernardi R, Rizzuto R, Tacchetti C, Pinton P, Pandolfi PP. PML regulates apoptosis at endoplasmic reticulum by modulating calcium release. Science. 2010 Nov 26;330(6008):1247-51

Reineke EL, Liu Y, Kao HY. Promyelocytic leukemia protein controls cell migration in response to hydrogen peroxide and insulin-like growth factor-1. J Biol Chem. 2010 Mar 26;285(13):9485-92

Van Damme E, Laukens K, Dang TH, Van Ostade X. A manually curated network of the PML nuclear body interactome reveals an important role for PML-NBs in SUMOylation dynamics. Int J Biol Sci. 2010 Jan 12;6(1):51-67

Geoffroy MC, Chelbi-Alix MK. Role of promyelocytic leukemia protein in host antiviral defense. J Interferon Cytokine Res. 2011 Jan;31(1):145-58

Kurahashi S, Hayakawa F, Miyata Y et al.. PAX5-PML acts as a dual dominant-negative form of both PAX5 and PML. Oncogene. 2011 Apr 14;30(15):1822-30

Qiu JJ, Chu H, Lu X, Jiang X, Dong S. The reduced and altered activities of PAX5 are linked to the protein-protein interaction motif (coiled-coil domain) of the PAX5-PML fusion protein in t(9;15)-associated acute lymphocytic leukemia. Oncogene. 2011 Feb 24;30(8):967-77

de Thé H, Le Bras M, Lallemand-Breitenbach V. The cell biology of disease: Acute promyelocytic leukemia, arsenic, and PML bodies. J Cell Biol. 2012 Jul 9;198(1):11-21

Ito K, Carracedo A, Weiss D, Arai F, Ala U, Avigan DE, Schafer ZT, Evans RM, Suda T, Lee CH, Pandolfi PP. A PML–PPAR-δ pathway for fatty acid oxidation regulates hematopoietic stem cell maintenance. Nat Med. 2012 Sep;18(9):1350-8

Rabellino A, Carter B, Konstantinidou G, Wu SY, Rimessi A, Byers LA, Heymach JV, Girard L, Chiang CM, Teruya-Feldstein J, Scaglioni PP. The SUMO E3-ligase PIAS1 regulates the tumor suppressor PML and its oncogenic counterpart PML-RARA. Cancer Res. 2012 May 1;72(9):2275-84

Scaglioni PP, Rabellino A, Yung TM, Bernardi R, Choi S, Konstantinidou G, Nardella C, Cheng K, Pandolfi PP. Translation-dependent mechanisms lead to PML upregulation and mediate oncogenic K-RAS-induced cellular senescence. EMBO Mol Med. 2012 Jul;4(7):594-602

Lo-Coco F, Avvisati G, Vignetti M, Thiede C, Orlando SM, Iacobelli S, Ferrara F, Fazi P, Cicconi L, Di Bona E, Specchia G, Sica S, Divona M, Levis A, Fiedler W, Cerqui E, Breccia M, Fioritoni G, Salih HR, Cazzola M, Melillo L, Carella AM, Brandts CH, Morra E, von Lilienfeld-Toal M, Hertenstein B, Wattad M, Lübbert M, Hänel M, Schmitz N, Link H, Kropp MG, Rambaldi A, La Nasa G, Luppi M, Ciceri F, Finizio O, Venditti A, Fabbiano F, Döhner K, Sauer M, Ganser A, Amadori S, Mandelli F, Döhner H, Ehninger G, Schlenk RF, Platzbecker U. Retinoic acid and arsenic trioxide for acute promyelocytic leukemia. N Engl J Med. 2013 Jul 11;369(2):111-21

Nisole S, Maroui MA, Mascle XH, Aubry M, Chelbi-Alix MK. Differential Roles of PML Isoforms. Front Oncol. 2013;3:125

Rabellino A, Scaglioni PP. PML Degradation: Multiple Ways to Eliminate PML. Front Oncol. 2013;3:60

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